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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/530,539	09/19/2005	Etsuro Ono	HER0071	5349

832 7590 06/08/2009

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EXAMINER	
SAJJADI, FEREYDOUN GHOTB	
ART UNIT	PAPER NUMBER
1633	
MAIL DATE	DELIVERY MODE
06/08/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/530,539	ONO ET AL.	
	Examiner	Art Unit	
	FEREYDOUN G. SAJJADI	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 March 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14,15,17,18,21-24 and 27-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14,15,17,18,21-24 and 27-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Status

Applicants' response of March 5, 2009, to the non-final Action dated September 5, 2008 has been entered. Claims 14, 15, 17 and 20-24 have been amended, claims 16, 19, 20, 25 and 26 cancelled and claims 28-35 newly added. Accordingly, claims 14, 15, 17, 18, 21-24 and 27-35 are pending in the Application and under current examination.

Withdrawn Claim Rejections - 35 USC § 112- Second Paragraph

Claims 14-16, 24, 25 and 27 were rejected as being indefinite, in the previous office action dated September 5, 2008. Applicants' cancellation of the claims 16 and 25 renders their rejections moot. Applicants have cancelled the indefinite language, obviating the grounds of rejection. Thus, the rejections are hereby withdrawn.

Withdrawn Rejections - 35 USC § 112- New Matter

Claim 14-27 were rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement and introducing new matter, in the previous office Action dated September 5, 2008. Applicants' cancellation of claims 16, 19, 20, 25 and 26 renders their rejections moot. Applicants' have deleted the limitation for a mouse immunoglobulin and further indicated the presence of support for V domain fusions in addition to VCC domain fusions to Fc crystallizable fragments in the specification. Accordingly the rejection is hereby withdrawn.

Maintained & New Claim Rejections - 35 USC § 112 – Written Description

Applicants' claim amendments have necessitated the following new grounds of rejection.

Claims 14, 15, 17, 18, 21-24 and 27 stand rejected and claims 28-35 are newly rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description

requirement. Applicants' cancellation of claims 16, 19, 20, 25 and 26 renders their rejections moot. The rejection set forth on pp. 5-6 of the previous office Action dated September 5, 2008 is maintained for claims 14, 15, 17, 18, 21-24 and 27, and is applied to newly added claims 28-35 for reasons of record.

Applicants' claim amendments replacing "cattle" with "bovine" fails to obviate the grounds of rejection. The instant claims encompass fusion transgenes comprising V domains of porcine or bovine and crystallizable Ig fragments of bovine, that confer resistance to infection by any pseudorabies (PRV) of bovine herpes virus (BHV-1); for which possession has not been demonstrated.

Applicants disagree with the rejection, and with reference to Milne, et al., Virology, 281, 315-328 (2001), argue that there is high degree of identity, structure/function relationships and predictability for the specified domains.

Applicants' arguments have been fully considered, but are not found persuasive. In response, it should be noted that the issue here is primarily with regard to the utilization of a V domain versus a VCC domain in creating a fusion transgene that confers resistance to PRV and BHV-1 infection in the transgenic animal. The "VCC domain" is the ectodomain of HveC. A "V domain" constitutes a subpart of the HveC extracellular domain (see Fig. 1 of Milne et al.). Thus, even ignoring amino acid differences in the HveC domains between pig and cow, a V domain and VCC domain are not structural or sequence equivalents, and as previously indicated, the specification only discloses the chimeric proteins containing the extracellular domain of Hvem (specifically, the mouse and porcine HveC) fused to the Fc portion of the human immunoglobulin IgG-1, introduced into the fertilized mouse embryo pronuclei (pp. 11 and 16), but does not describe the structure or functional nature of any chimeric proteins containing only the V domain of nectin-1 or HveC from porcine or bovine, capable of conferring resistance to PRV or BHV-1 virus infections, that would include peptides yet to be discovered. Because the instant specification is silent on which parts of nectin-1 from the numerous species of mammals claimed would retain such an activity, possession of the numerous species other than porcine VCC has not been demonstrated at the time of the invention. Thus it is maintained that the written description requirement is not satisfied for the claimed genus of fusion proteins or mammals.

The previous rejection additionally indicated that possession has further not been demonstrated for fusion proteins between the V or VCC domains or nectin-1 and the Ig crystallizable fragments from various species. Applicants should note that instant claims fail to limit the crystallizable fragment to the crystallizable Fc fragment indicated in the specification. As Applicants previously stated, that the specification (p. 6, lines 24 to 37) discloses a fusion of comprising the extracellular domain of porcine HveC protein. In particular, the production of a fusion protein having an extra-cellular domain of the porcine receptor HveC that binds to the PRV virus and the crystallisable portion Fc of the human immunoglobulin IgG-1; further stating that the inventors contemplated production of a transgene encoding a fusion protein of the extracellular domain of porcine or bovine HveC or nectin-1 and the crystallisable portion Fc of the mammalian IgG-1, for example, p. 10, lines 21-26. As such, the structure/function relationships of the various species combinations remains unknown, that would further retain an ability to confer resistance to an infection by any PRV or BHV-1 viruses.

Thus, the rejection is maintained for claims 14, 15, 17, 18, 21-24 and 27, and is applied to newly added claims 28-35 for reasons of record, and the preceding commentary.

Maintained & New Claim Rejections - 35 USC § 112- Scope of Enablement

Applicants' claim amendments have necessitated the following new grounds of rejection.

Claims 14, 15, 17, 18, 21-24 and 27 stand rejected under 35 U.S.C. §112, first paragraph, as failing to provide an enablement for the full scope of the invention. Applicants' cancellation of claims 16, 19, 20, 25 and 26 renders their rejections moot. The rejection set forth on pp. 6-8 of the previous office action dated September 5, 2008 is maintained in modified form for claims 14, 15, 17, 18, 21-24 and 27, and is applied to newly added claims 28-35 for reasons of record.

In view of the Declaration (under 37 CFR 1.132) provided by Dr. Pierre Cherel, the enabled scope previously indicated, has been broadened to include a process for producing a mouse or porcine resistant to infection by PRV, whose genome comprises a transgene recombinant DNA including the coding sequence of a fusion protein of the VCC domain of

porcine nectin-1 and the crystallisable Fc fragment of an immunoglobulin selected from the group consisting of human or porcine immunoglobulin operably linked to a promoter.

The specification does not reasonably provide an enablement for a process for producing mice, pig and bovine resistant to infection by PRV or BHV-1, whose genome comprises a fusion protein of the V or VCC domains of porcine or bovine, and the crystallisable fragment of an immunoglobulin selected from the group consisting of human, porcine, or mouse immunoglobulin operably linked to a promoter, as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicants traverse the rejection, citing the data provided in the declaration by Dr. Cherel, from two transgenic pig lines exhibiting 10% and 50% mortality rates when infected with the PRV virus, and argue that such provides efficacy of the methods, without the problems discussed in the office Action. Applicants' arguments have been fully considered, but are not found persuasive.

In response, it should be noted that the enabled scope of the claimed invention has been expanded, as set forth above, and that the two pig lines described in the Declaration were generated with a transgene construct containing the porcine VCC domain of HveC fused with human Fc, and that the infection data was limited to PRV. Thus, the data presented in the Declaration is not commensurate in scope with the full breadth of the instantly claimed invention that includes bovines resistant of PRV or BHV-1, or mice, pigs and bovines whose genome comprises a transgene encoding a fusion between the V domain of porcine or bovine nectin-1, and any crystallisable fragment of human, porcine or bovine immunoglobulin.

Applicants cite U.S. Patent No; 5,633,076 disclosing a method of producing transgenic bovine, and that the skilled artisan could practice the full scope of the claimed subject matter. Such is not found persuasive, because the issue is not the ability to generate a transgenic bovine, but whether generating a bovine or mouse or pig whose genome comprises a transgene encoding a fusion between only the V domain of porcine or bovine nectin-1, and any crystallisable fragment of human, porcine or bovine immunoglobulin, that in turn is resistant to PRV or BHV-1 virus infection.

Applicants refer to arguments in the Declaration that random insertion of the transgene did not affect the efficiency of the subject methods. Such is not found persuasive, because the 10% and 50% survival data are evidence of variability inherent in producing transgenic lines, due to gene copy number, background, linkage and epistasis, as previously discussed. In the instant case, the transgenes of interest are required to provide resistance to PRV or BHV-1 viruses in various species of animals, based on observations in a few lines of transgenic mice and pigs, that each show variations to PRV infection, even when the same transgene limited to one encoding a fusion protein of the VCC domain of porcine nectin-1 and the crystallisable Fc fragment of an immunoglobulin selected from the group consisting of human or porcine immunoglobulin.

As previously indicated, resistance to infection is clearly dependent on both the type of HveC receptor and the particular alphaherpesvirus. The specification fails to disclose either a transgenic bovine, or porcine expressing the various claimed V domain or VCC domain fusion proteins, and therefore any resistance of these transgenic animals to PRV or BHV-1 virus infections remains unknown and would have to be determined by further experimentation.

Thus, the rejection is maintained in modified form for claims 14, 15, 17, 18, 21-24 and 27, and is applied to newly added claims 28-35 for reasons of record, and the foregoing commentary.

Maintained & New Claim Rejections - 35 USC § 103

Applicants' claim amendments have necessitated the following new grounds of rejection.

Claims 14, 15, 17, 18, 23 and 27 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Fiume et al. (U.S. Patent No.: 6,469,155, filed Nov. 9, 1999), in view of Bujard et al. (US. Patent No.: 5,866,755, Feb. 2, 1999). Applicants' cancellation claims of 20, 25 and 26 renders their rejections moot. The rejection set forth on pp. 12-13 of the office action dated November 1, 2006, pp. 7-8 of the office action dated July 25, 2007 and pp. 8-10 of the previous Action dated September 5, 2008 is maintained for claims 14, 15, 17, 18, 23 and 27, and further applied to claim 21 and newly added claims 29-32 and 35 for reasons of record and the expanded enabled scope.

The previous office Actions indicated the teachings of the applied references as follows:

Fiume et al. state that alphaherpesviruses include HSV-1, HSV-2, PRV, and BHV-1 infect a variety of cells (column 1) and describe various fusion proteins between various segments of HIgR (herpesvirus immunoglobulin-like receptor) and the Fc portion of human IgG1 (Abstract and column 4). The authors teach that HIgR, and/or its splice variant HveC, are involved in cell to cell spread of HSV (column 3, last paragraph). Specifically described are sVCC(PVRα)-Fc containing the soluble V domains of HIgR (column 4 and Example 4), in addition to the discovery in the prior art that a soluble form of HveC containing the entire ectodomain is capable of such binding (column 17). Fiume et al. further state that an object of their invention is to provide cells that are resistant to infection by HSV-1, HSV-2 and BHV-1 (column 1). Fiume et al. state that an embodiment of their invention is the construction of transgenic mice expressing the alphaherpesvirus receptors that mediate HSV and BHV-1 entry, from transgenes to produce a mouse model system for the viral infections (column 3); thus providing the motivation to use their constructs as transgenes in transgenic mice.

Bujard et al. describe transgenic animals carrying a transgene comprising a nucleic acid molecule encoding a fusion protein composed of two polypeptides (Abstract). The authors describe the creation of a transgenic animal by introducing a nucleic acid encoding the fusion protein (linked to appropriate regulatory elements) into the male pronuclei of fertilized oocytes by microinjection and allowing the oocytes to develop in a pseudopregnant female foster animal. Additionally stating that methods for generating transgenic animals such as mice have become conventional in the art (column 15). The generation of mice expressing a fusion protein is set forth in Example 6. Therefore, a person of ordinary skill in the art would have been motivated to combine the teachings of Fiume et al. and Bujard et al. to produce transgenic mice expressing the HveC-Fc fusion protein. A person of ordinary skill in the art, having combined the HveC-Fc construct of Fiume et al. as a transgene, with the method of generating transgenic mice expressing a fusion protein as taught by Bujard et al., would be able to practice the instantly claimed method, resulting in the claimed transgenic animal of the instant invention, said transgenic animal further capable of expressing an alphaherpesvirus receptor, with a reasonable expectation of success.

It should be noted that Bujard et al. further state that the transgenic animal of their

invention may additionally include a pig (column 3, lines 15-17). Similarly, Fiume et al. disclose a transgenic pig (column 33, lines 52-53).

Applicants traverse the rejection, argue that the Bujard reference does not appear to be cited for particular relevance. Applicants' arguments have been fully considered, but are not found persuasive.

As is clear from the foregoing, the Bujard reference provides for the reduction to practice of the transgenic animals contemplated by Fiume et al., expressing a fusion protein. Thus, the reference has particular relevance to the instant rejection.

Applicants argue that Fiume does not teach, suggest, or otherwise show or make obvious transgenic mice containing a transgene encoding the specified fusion protein of claim 14. Such is not found persuasive, because as previously indicated, the object of the Fiume patent is to utilize HIGR and related domains which bind the glycoprotein D of herpes simplex virus in preventing infection by said virus (Title and Abstract). Fiume et al. describe various fusion proteins between various segments of HIgR (herpesvirus immunoglobulin-like receptor) and the Fc portion of human IgG1 (Abstract and column 4). Specifically described are sVCC(PVRα)-Fc containing the soluble V domains of HIgR (column 4 and Example 4), in addition to the discovery in the prior art that a soluble form of HveC containing the entire ectodomain is capable of such binding (column 17). Fiume et al. further state that an object of their invention is to provide cells that are resistant to infection by HSV-1, HSV-2 and BHV-1 (column 1). Fiume et al. state that an embodiment of their invention is the construction of transgenic mice expressing the alphaherpesvirus receptors that mediate HSV and BHV-1 entry, from transgenes to produce a mouse model system for the viral infections (column 3). Thus, utilizing domains or parts of a nectin-1 outside its physiological context, and meeting the limitations of the instant claims.

Applicants argue that Fiume teaches a transgenic mouse that produces the full-length, functional, transmembrane receptor for herpes virus, which renders the mice hyper-sensitive to infection by herpesvirus. In response, it should be noted that such is one embodiment of Fiume et al.'s invention. Fiume et al. specifically describe various fusion proteins between various segments of HIgR (herpesvirus immunoglobulin-like receptor) and the Fc portion of human IgG1 (Abstract and column 4). Specifically described are sVCC(PVRα)-Fc containing the soluble V

domains of HIgR (column 4 and Example 4), in addition to the discovery in the prior art that a soluble form of HveC containing the entire ectodomain is capable of such binding (column 17).

Applicants argue that Fiume also constructed fusion proteins comprising segments of the extracellular portion of the receptor to identify specific binding domains, so those domains could be specifically targeted for block by antibodies in an attempt to prevent binding. And unlike Fiume, the subject fusion proteins produced by animals are soluble and non-membrane bound. Such is not found persuasive because the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). It should be noted however, that Fiume et al. specifically disclose a transgenic animal expressing an expressed transgene encoding a virus receptor or a binding domain of the virus receptor and determining whether the transgenic animal is protected from infection from herpes virus infection, in conjunction with a vaccine (column 33, lines 59-64).

As Fiume et al. expressly describe soluble sVCC(PVRα)-Fc containing the soluble V domains of HIgR (column 4 and Example 4), in addition to the discovery in the prior art that a soluble form of HveC containing the entire ectodomain is capable of such binding (column 17), as well as transgenes in animals expressing only the binding domains of the virus receptor (column 33), Applicants' arguments regarding transmembrane or membrane-bound receptors and that fusion proteins are not produced by a transgenic mouse, are without ground.

Therefore the rejection is maintained for claims 14, 15, 17, 18, 23 and 27, and further applied claims 21, 29-32 and 35 for reasons of record and the foregoing commentary.

Conclusion

Claims 14, 15, 17, 18, 21-24 and 27-35 are not allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. The claims are drawn to the same invention claimed earlier in the application and would have been finally rejected on the grounds and art of record in the next Office Action if

they had been entered earlier in the application. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR§1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to FEREYDOUN G. SAJJADI whose telephone number is (571)272-3311. The examiner can normally be reached on 6:30 AM-3:30 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Fereydoun G Sajjadi/
Primary Examiner, Art Unit 1633